REMARKS

Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 74-76, 92-94, 123, 124, 127-133 and 135-139 are pending. Claim 127 is amended herein. Claim 127 is amended herein to more distinctly claim the subject matter. Basis for the amendment is found throughout the specification (e.g., see page 12, lines 1-6 and page 10, lines 12-27). No new matter is added.

REJECTION OF CLAIMS 127-133, 135 and 137-139 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 127-133, 135 and 137-139 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The claims allegedly contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the patent applicant had possession of the claimed subject matter at the time of filing of the application. The Examiner alleges that the recited passage does not define or limit the four bases. Applicant respectfully traverses the rejection.

RELEVANT LAW

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject mater at the time of filing of the application *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563-64, 19 USPQ2d at 1117.

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific

compound [claimed embodiment] *Vas-Cath, Inc. v. Mahurkar*, at 1115, quoting *In re Ruschig*, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991).

THE CLAIMS

Claim 127 is directed to an array of nucleic acid probes, where each probe includes a single-stranded portion at one terminus, a double-stranded portion at the opposite terminus, and a variable nucleotide sequence within the single-stranded portion, where the probes are divided into four subsets and for each subset, a selected nucleotide base of the four bases of the nucleic acid occupies a defined number of positions in each probe and all other nucleotide bases except the selected nucleotide base occupy the remaining positions. Claims 128-133, 135 and 137-139 ultimately depend from claim 127 and are directed to various embodiments thereof.

ANALYSIS

The rejection as applied to the recitation "wherein the selected nucleotide base is adenosine-5'-phosphate, deoxyadenosine-5'-phosphate, deoxythymidine-5'-phosphate, uridine-5'-phosphate, guanine-5'-phosphate, deoxyguanosine-5'-phosphate, cytidine-5'-phosphate or deoxycytidine-5'-phosphate" in claim 127 is obviated by the amendment of claim 127 herein. Applicant respectfully disagrees with the Examiner that the specification specifically teaches use of ddNTP in the array of probes as claimed.

1. "a selected nucleotide base of the four bases of the nucleic acid"

Applicant respectfully submits that, in light of the teachings of the specification, one skilled in the art would understand that the recitation "a selected nucleotide base of the four bases of the nucleic acid" refers to selecting one of the ribonucleotides adenosine-5'-phosphate, uridine-5'-phosphate, cytidine-5'-phosphate and guanine-5'-phosphate for a ribonucleic acid (RNA) molecule or to selecting one of the deoxynucleotides deoxyadenosine-5'-phosphate, deoxythymidine-5'-phosphate, deoxyguanosine-5'-phosphate and deoxycytidine-5'-phosphate for a deoxyribonucleic acid (DNA) molecule. First, it is known to one of skill in the art that a nucleic acid molecule is made up of four bases. The "four bases" in a ribonucleic acid (RNA) molecule include the ribonucleotides adenosine-5'-phosphate, uridine-5'-phosphate, cytidine-5'-phosphate and guanine-5'-phosphate and that

the "four bases" found in a deoxyribonucleic acid (DNA) molecule include the deoxy-nucleotides deoxyadenosine-5'-phosphate, deoxythymidine-5'-phosphate, deoxyguanosine-5'-phosphate and deoxycytidine-5'-phosphate (*e.g.*, see Zubay, *Biochemistry*, page 662 (1983), a copy of which was supplied in the previous response). Second, the specification teaches that using the theory of degenerated probes taught by Macevicz allows the reduction in the size of the array of probes, resulting in savings in time and expense. For example, see page 1, line 16 through page 12, line 9, which recites:

> A principle advantage of this probe is in its structure. Hybridization of the target nucleic acid is encouraged due to the favorable thermodynamic conditions established by the presence of the adjacent double-strandedness of the probe. An entire set of probes contains at least one example of every possible random nucleotide sequence.
>
> By way of example only, if the random portion consisted of a four nucleotide sequence (R=4) of adenine, guanine, thymine, and cystosine, the total number of possible combinations (4^R) would be 4^4 or 256 different nucleic acid probes. If the number of nucleotides in the random sequence was five, the number of different probes within the set would be 4^5 or 1,024. This becomes a very large number indeed when considering sequences of 20 nucleotides or more.
>
> However, to determine the complete sequence of a nucleic acid target, the set of probes need not contain every possible combination of nucleotides of the random sequence to be encompassed by the method of this invention. This variation of the invention is based on the theory of degenerated probes proposed by S. C. Macevicz (International Patent Application, US89-04741, published 1989, and herein specifically incorporated by reference). The probes are divided into four subsets. In each, one of the four bases is used at a defined number of positions and all other bases except that one on the remaining positions. Probes from the first subset contain two elements, A and non-A (A=adenosine). For a nucleic acid sequence of length k, there are $4(2^k -1)$, instead of 4^k probes. Where k=8, a set of probes would consist of only 1020 different members instead of the entire set of 65,536. The savings in time and expense would be considerable.

The array of claim 127 recites elements of an array of degenerate probes. The probes of the array are divided into four subsets and for each subset, a selected nucleotide base of the four bases of the nucleic acid occupies a defined number of positions in each probe and all other nucleotide bases except the selected nucleotide base occupy the remaining positions. Applicant respectfully submits that the theory of degenerate probes is set forth, for example, in International Patent Application PCT/US89/04741, which published as WO 90/04652. The teachings are incorporated by reference in the instant application. The teachings of Macevicz expand on the recitation "four subsets" recited in the instant application. For example, Macevicz teaches on page 3, line29 through page 4, line 9 recites:

In one embodiment of the invention, the set of probes comprises four subsets. Each of the four subsets contains probes representing every possible sequence, with respect to the size of the probe (which is predetermined), of only one of the four bases. For example, the first subset can contain probes where every possible sequence of G is represented; the second subset can contain probes where every possible sequence of T is represented; and so on for C and A. If the probes were each 8 bases long, a member probe of the adenosine subset can be represented as follows:

$$3'\text{-}AA\begin{bmatrix}C\\G\\T\end{bmatrix}\begin{bmatrix}C\\G\\T\end{bmatrix}A\begin{bmatrix}C\\G\\T\end{bmatrix}\begin{bmatrix}C\\G\\T\end{bmatrix}A\text{-}5'$$

Formula I

The symbol $\begin{bmatrix}C\\G\\T\end{bmatrix}$ means that any of the bases C, G, or T may occupy the position where the symbol is located. Thus, the above probe has a multiplicity, or degeneracy, of lxlx3x3xlx3x3xl, or 81. When it is clear from the context which subset is being considered, the above notation will be simplified to AA00A00A, where A represents deoxyadenosine and 0 represents the absence of deoxyadenosine.

Thus, the specification conveys with reasonable clarity to the skilled artisan that, as of the filing date sought, Applicant was in possession of the array of probes as instantly claimed.

2. Use of ddNTP

The Examiner alleges that "the specification (on page 13), which immediately follows the cited passage [recited for providing basis for the a selected nucleotide base of the nucleic acid occupying a defined number of positions in each probe and all other nucleotide bases except the selected nucleotide base occupying the remaining positions], specifically teaches use of ddNTP. Applicant respectfully submits that this is not an accurate characterization of the teachings of the specification. First, the paragraph of the specification that teaches use of ddNTP does not "immediately follow" the recited paragraph. There is an intervening paragraph. Second, the paragraph on page 13 that teaches use of ddNTP is not discussing the array of degenerate probes. The discussion in the paragraph (page 12, line 13 through page 13, line 2) immediately following the recited paragraph discusses hybridization and the paragraph following that (page 13, lines 3-24), which includes the teaching directed to use of ddNTP, discusses methods for determining the sequence of the nucleic acid probe. For clarity, the two paragraphs in the specification that "immediately follow" the recited paragraph discussing arrays of degenerated probes is set forth below and recites:

> Hybridization between complimentary bases of DNA, RNA, PNA, or combinations of DNA, RNA and PNA, occurs under a wide variety of conditions

such as variations in temperature, salt concentration, electrostatic strength, and buffer composition. Examples of these conditions and methods for applying them are described in Nucleic Acid Hybridization: A Practical Approach (B. D. Hames and S. J. Higgins, editors, IRL Press, 1985), which is herein specifically incorporated by reference. It is preferred that hybridization takes place between about 0°C and about 70°C, for periods of from about 5 minutes to hours, depending on the nature of the sequence to be hybridized and its length. For example, typical hybridization conditions for a mixture of two 20-mers is to bring the mixture to 68°C and let cool to room temperature (22°C) for five minutes or at very low temperatures such as 2°C in 2 microliters. It is also preferred that hybridization between nucleic acids be facilitated using buffers such as saline, Tris-EDTA (TE), Tris-HCl and other aqueous solutions, certain reagents and chemicals. Preferred examples of these reagents include single-stranded binding proteins such as Rec A protein, T4 gene 32 protein, E. coli single-stranded binding protein, and major or minor nucleic acid groove binding proteins. Preferred examples of other reagents and chemicals include divalent ions, polyvalent ions, and intercalating substances such as ethidium bromide, actinomycin D, psoralen, and angelicin.

The nucleotide sequence of the random portion of each probe is determinable by methods which are well-known in the art. Two methods for determining the sequence of the nucleic acid probe are by chemical cleavage, as disclosed by Maxam and Gilbert (1977), and by chain extension using ddNTPs, as disclosed by Sanger et al. (1977), both of which are herein specifically incorporated by reference. Alternatively, another method for determining the nucleotide sequence of a probe is to individually synthesize each member of a probe set. The entire set would comprise every possible sequence within the random portion or some smaller portion of the set. The method of the present invention could then be conducted with each member of the set. Another procedure would be to synthesize one or more sets of nucleic acid probes simultaneously on a solid support. Preferred examples of a solid support include a plastic, a ceramic, a metal, a resin, a gel, and a membrane. A more preferred embodiment comprises a two-dimensional or three- dimensional matrix, such as a gel, with multiple probe binding sites, such as a hybridization chip as described by Pevzner et al. (J. Biomol. Struc. & Dyn. 9:399-410, 1991), and by Maskos and Southern (Nuc. Acids Res. 20:1679-84, 1992), both of which are herein specifically incorporated by reference. Nucleic acids are bound to the solid support by covalent binding such as by conjugation with a coupling agent, or by non-covalent binding such as an electrostatic interaction or antibody-antigen coupling. Typical coupling agents include biotin/streptavidin, Staphylococcus aureus protein A/IgG antibody F_c fragment, and streptavidin/protein A chimeras (T. Sano and C. R. Cantor, Bio/Technology 9:1378-81, 1991).

Thus, the section of the specification on page 13 that teaches the use of ddNTPs recited by the Examiner is directed to the Sanger method of determining the sequence of the nucleic acid probe by chain extension using ddNTPs. The cited section does not teach or suggest selecting a ddNTP to occupy a defined number of positions in each probe. Applicant respectfully requests reconsideration and withdrawal of the rejection.

THE REJECTION OF CLAIMS 127-133 AND 135-139 UNDER 35 U.S.C. §102(b)

Claims 127-133 and 135-139 are rejected under 35 U.S.C. §102(b) as anticipated by Hornes *et al.* (WO 90/06045, published 14 June 1990) because Hornes *et al.* allegedly discloses every element of the claimed array. The Examiner alleges that the non-hybridized target of Hornes *et al.* is a "variable region," the oligo-dT is a "double-stranded portion," that a biotinylated nucleotide at the end or an incorporated ddNTP is a "selected nucleic acid base that occupies a defined number of positions" and "non-biotinylated A, T, C and G" are "all other bases" that occupy the remaining positions, and that page 15 discloses dividing the arrays into for subsets. This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE CLAIMS

See related section above.

Disclosure of Hornes *et al.*

Hornes *et al.* discloses magnetic particles that have a plurality of oligonucleotide probes that are either directly attached to the magnetic particle or attached via a double-stranded piece of DNA (page 2, lines 9-22). The probes include an oligo-dT sequence and optionally restriction enzyme sites (page 2, lines 25-31). In one embodiment, a DNA molecule having a sequence complementary to a known sequence of a target nucleic acid molecule is hybridized to the probe (having an oligo-dT sequence) via a poly-dA tail on the DNA sequence, and a different labeled "probe" is hybridized to a different sequence of the

nucleic acid molecule, forming a ternary complex (page 13, lines 1-11). Hornes *et al.* discloses standard Sanger sequencing reactions (page 14, lines 2-36). Hornes *et al.* discloses a method of sequencing single-stranded nucleic acids that includes dividing particles that include single-stranded DNA or RNA oligonucleotide to be sequenced into four aliquots and adding to each aliquot a polymerase, mixed nucleotide triphosphates and a different dideoxynucleoside triphosphate for each aliquot (page 15, lines 15-37).

Differences between the claimed subject matter and the disclosure of Hornes *et al.*

Hornes *et al.* does not disclose an array of probes where a selected nucleotide base of the nucleic acid occupies a defined number of positions in each probe and all other nucleotide bases except the selected nucleotide base occupy the remaining positions. Hornes *et al.* discloses incorporating a biotinylated base at the end of the probe as a coupling agent, or incorporating a terminal dideoxynucleoside in the probe to produce a series of labeled DNA strands having different chain lengths and ending with a particular dideoxy base. The Examiner alleges that the terminal biotinylated base or dideoxynucleoside is the same as the "selected base" occupying a defined number of positions as instantly claimed and that "all other bases" include non-biotinylated A, T, C, and G. The claims, amended for clarity, recite that the "selected nucleotide base" is selected from one of the four bases of the nucleic acid molecule. A discussed above, it is recognized by one of skill in the art that that the "four bases" in an RNA molecule include the ribonucleotides adenosine-5'-phosphate, uridine-5'-phosphate, cytidine-5'-phosphate and guanine-5'-phosphate and that the "four bases" found in a DNA molecule include the deoxynucleotides deoxyadenosine-5'-phosphate, deoxythymidine-5'-phosphate, deoxyguanosine-5'-phosphate and deoxycytidine-5'-phosphate.

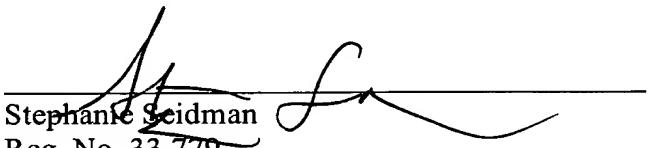
Hornes *et al.* does not disclose an array of probes where the array is divided into four subsets and for each subset, one of adenosine-5'-phosphate, uridine-5'-phosphate, cytidine-5'-phosphate or guanine-5'-phosphate is selected and occupies a defined number of positions in each probe and all other nucleotide bases except the selected base occupy the remaining positions. Hornes *et al.* discloses on page 15 that its magnetic particles include a single-stranded oligonucleotide to be sequenced and that these particles are divided into four aliquots. To each of these aliquots a different dideoxynucleoside triphosphate is added. Hornes *et al.* does not disclose an array of probes divided into four subarrays, where for each subarray, one of the four bases of the nucleic acid molecule is selected to occupy a defined number of positions and the other positions are occupied by bases other than the selected base (for

example, the adenosine subset would have adenosine in a defined number of positions and non-adenosine bases would occupy the remaining positions). Hence, Hornes *et al.* does not disclose every element of claim 127. Therefore, because Hornes *et al.* does not disclose every element of claim 127, Hornes *et al.* does not anticipate claims 127-133 and 135-139.

* * *

In view of the above, examination of the application on the merits and allowance is respectfully requested.

Respectfully submitted,



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